New Drug Successfully Converts Atrial Fibrillation

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NEW ORLEANS — The novel antiarrhythmic agent RSD1235 effectively converted atrial fibrillation to sinus rhythm in a median of just 11 minutes in its initial phase III clinical trial, Dennis Roy, M.D., reported at the annual meeting of the Heart Rhythm Society.

The drug's safety profile also was excellent. There were fewer significant adverse events than with placebo—and most importantly, no cases of torsade de pointes, added Dr. Roy of the Montreal Heart Institute.

RSD1235 is a frequency-dependent sodium and early-activating potassium channel blocker with multiple electrophysiologic effects. It is atrial selective, with no effect upon ventricular repolarization, a highly desirable property in a drug for the treatment of atrial arrhythmias.

Dr. Roy reported on 336 patients with atrial fibrillation of 3 hours' to 45 days' duration who were randomized 2:1 to RSD1235 or placebo in the double-blind Atrial Arrhythmia Conversion Trial 1 (ACT 1). Patients who didn't convert within 15 minutes after completion of the initial IV infusion of 3 mg/kg given over 10 minutes received a second one, this time at 2 mg/kg.

The primary end point in ACT 1 was conversion to sinus rhythm within 90 minutes of treatment in the 220 patients with atrial fibrillation of up to 7 days' duration. The rate was 52% in the RSD1235 group, compared with just 4% with placebo. Only 1 of the 75 RSD1235-treated patients who converted within 90 minutes relapsed by 24 hours.

It is clearly a drug for recent-onset patients. The conversion rate in subjects with atrial fibrillation of 8-45 days' duration was 8% with RSD1235 and 0% for placebo.

The chief side effect associated with RSD1235 was impairment of taste, or dysgeusia, which affected 30% of treated patients but lasted an average of only 12 minutes. Second most common were sneezing fits, which affected 16% of patients and lasted 3 minutes, followed by paresthesia, affecting 11% for an equally brief period. Recurrence of atrial fibrillation within 30 days occurred in 6% of the RSD1235 group.

Additional phase III trials known as ACT 2 and ACT 3 are well underway. They include patients with atrial flutter as well as those with atrial fibrillation arising after cardiac surgery.

Dr. Roy is a consultant to and equity holder in Cardiome Pharma Corp., the developer of RSD1235.

Elsewhere at the meeting, in a state-of-the-art talk on the prospects for new drugs for atrial fibrillation, Peter F. Kowey, M.D., called the results of ACT 1 encouraging. Also encouraging is the program to develop an oral formulation of RSD-1235 designed for long-term maintenance of sinus rhythm following conversion of atrial fibrillation.

Many other drugs in development show varying degrees of promise. These include the atrial-selective agent AZD7009, gap junction modulators designed to restore pathologic defects in intercellular conduction, 5-hydroxytryptamine antagonists such as piboserod, and ATI-2042, a structural analog of amiodarone with similar electrophysiologic effects but less toxicity.

There is a great need for new agents for atrial fibrillation because the vast majority of affected patients will never be candidates for invasive catheter ablation procedures. And most of them would prefer to be on effective rhythm- than rate-control medications, said Dr. Kowey, professor of medicine at Jefferson Medical College, Philadelphia.

He couldn't resist the opportunity to toss a few zingers at colleagues in the ablation camp.

"For some reason, when ablationists get up and talk about what's happening in atrial fibrillation, they always tell us, 'Yeah, it's not so good right now, but it's going to get a whole lot better—and by the way, drugs suck.' Nobody gives the people on the drug side credit for the fact that, gee, we might get better, too. I mean, we're not exactly sitting on our hands here," he said.

"There's a tremendous amount of activity going on in the drug development world to understand the arrhythmia mechanisms better, which the ablationists don't seem to really care as much about, and also to try to find specific probes to treat those arrhythmias using new chemical entities that are not only more effective but safer," Dr. Kowey added. ■

Classic Cox-Maze Surgery for AF: Perhaps Not All It's Cut Out to Be?

SAN FRANCISCO — The classic cut-and-sew Cox-Maze procedure is considered the definitive method for ablation of atrial fibrillation—the benchmark therapy to which a host of emerging innovative percutaneous and surgical ablative approaches must be compared. So just how good is it?

Not as great as open-heart surgeons and their patients would like to think, according to A. Marc Gillinov, M.D., surgical director of the atrial fibrillation (AF) program at the Cleveland Clinic Foundation.

Indeed, his retrospective study of 263 patients who underwent combined mitral valve surgery and a Cox-Maze procedure at the clinic showed ablation failure rates of 17% and 34% at 1 year and 3 years, respectively, he reported at the annual meeting of the American Association for Thoracic Surgery.

Ablation failure was defined by one or more episodes of AF occurring more than 6 months post surgery. Operative mortality was 1.9%. At 5 years, the prevalence of AF was 9%. Recurrent AF was electrically documented via a total of 2,367 ECGs during a median 2.6 years of follow-up.

Independent risk factors for recurrence of AF following Cox-Maze surgery were longer preoperative duration of the arrhythmia, greater left atrial size, patient age, and left ventricular mass index, Dr. Gillinov continued.

"We draw certain inferences from these data. It's possible that results would be enhanced by earlier operation after the development of atrial fibrillation. In addition, left atrial size reduction may improve results in patients with left atrial dilatation. Perhaps most importantly, these data teach us that close long-term follow-up of heart rhythm is necessary after ablation," he observed.

The recurrence rates documented in this study are actually underestimates; as yet, no method exists for continuously monitoring heart rhythm month in and month out. It's sorely needed, Dr. Gillinov said.

"This is really the only methodology that will enable us to state with absolute confidence that at least until the point of follow-up we have achieved a cure," he noted. "In addition, continuous monitoring will enable us to calculate the atrial fibrillation burden—the percentage of time a given patient is in atrial fibrillation—and we believe that this will turn out to be a clinically useful index of success or failure of the procedure."

Although there was no control group in this series, 74% of participants presented for surgery in permanent AF—that is, continuous AF that was always present. Three years after surgery, only 10% of patients were on antiarrhythmic agents.

Dr. Gillinov said that although very few patients in this series underwent left atrial size reduction, in the last year or two, surgeons at the Cleveland Clinic have become much more aggressive in pursuing this strategy.

"What we do now is, if the left atrium is 6 cm or greater as measured by echo in any dimension, we will cut out a portion," the surgeon explained.

All patients underwent removal of their left atrial appendage—the most common source of thromboemboli—at the time of the Cox-Maze procedure. Dr. Gillinov and his colleagues have been studying these appendages and the left atria to which they were attached, for more than a decade in an effort to better understand the arrhythmia.

"What we find is that in people with very-long-term atrial fibrillation—which correlates with an enlarged left atrium and permanent atrial fibrillation—their atria have an intense inflammatory reaction, scar, and fibrosis. I think what that patient brings to the operating room may make it such that we can never restore sinus rhythm, at least not permanently, even with the operation done correctly," he said. "A strategy of long-term antiarrhythmic therapy may improve our results in those patients." ■

Mental Distress Is Strong Risk Factor for AF Onset

NEW ORLEANS — Anxiety and other forms of psychological distress constitute a potent independent risk factor for development of new-onset atrial fibrillation in patients with chronic stable coronary artery disease, Charles M. Blatt, M.D., reported at the annual scientific sessions of the American Heart Association.

The relationship is dose dependent. The higher a CAD patient's level of anxiety, depression, somatization, or hostility, the greater the long-term risk of developing atrial fibrillation, explained Dr. Blatt of Harvard Medical School, Boston, and director of research at the Lown Cardiovascular Research Foundation, Brookline, Mass.

He reported on 354 men and 95 women with chronic stable CAD who were prospectively followed for an average of 5 years. Participants in the ongoing observational study are being assessed annually for various forms of psychological distress using the 92-item Kellner's Symptom Questionnaire.

The incidence of atrial fibrillation in patients in the lowest Kellner quartile for total psychological distress was 2 cases per 1,000 person-years, compared with 16 cases per 1,000 person-years in those in the fourth quartile. Similarly, incidence of atrial fibrillation among patients in the lowest quartile for anxiety was 3 cases per 1,000 person-years, versus 16 in those in the highest quartile.

After adjustment for the standard risk factors for atrial fibrillation, including gender and age, patients in the second through fourth quartiles in terms of anxiety level had a 2.1-fold greater risk of developing atrial fibrillation for each quartile increase.

Each quartile of depression level was associated with a 1.7-fold greater risk of developing atrial fibrillation compared with that of patients in the bottom quartile in terms of depression. The risk of atrial fibrillation increased by an additional 50% with each of the second through fourth quartiles of somatization, and by 60% with each quartile of scoring on hostility.

Patients in the second quartile for total psychological distress had an adjusted 2.3-fold increased risk of developing atrial fibrillation compared with the patients in the lowest quartile. ■